THE APPROACH TO THE TREATMENT OF HYPERTENSIVE PATIENTS WITH RENAL PARENCHYMAL DISEASE*

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SINCE Richard Bright[1] first described the association between renal disease and hypertension in 1836, the question of cause and effect has often been debated. While this may be unanswerable in some cases, benign essential hypertension rarely leads to renal failure unless it enters the malignant or accelerated phase. Most patients with renal parenchymal disease, however, develop hypertension, which suggests that the renal disorder somehow causes the blood pressure elevation. In addition, systemic diseases that can lead to renal failure, e.g., diabetes mellitus and systemic lupus erythematosus, are often accompanied by severe hypertension. In the past, many hesitated to treat hypertensive patients who had renal insufficiency because of the fear of aggravating the renal dysfunction. We now know that whether the hypertension is antecedent, coincident, or consequent to the renal disease it should be treated. To do so may improve renal function, and not to do so may accelerate the decline.

PATHOGENESIS OF HYPERTENSION IN RENAL DISEASE

Many renal diseases are associated with hypertension whether or not renal insufficiency is present. Acute glomerulonephritis is usually accompanied by hypertension, even when renal function may be normal. Unilateral renal diseases, such as unilateral pyelonephritis, segmental hypoplasia

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of the kidney (the Ask-Upmark abnormality), obstruction, renovascular abnormalities, and renin secreting tumors are associated with hypertension. In fact, the hypertension may be cured by unilateral nephrectomy despite some consequent loss of renal function.[2-9]

Acute and chronic glomerulonephritis appear to cause hypertension by increasing salt and water retention. On the other hand, unilateral renal disease often causes hypertension by a renin-dependent mechanism. Most hypertension of chronic renal disease is volume dependent with an elevated cardiac output.[10-12] Hypertension is the product of cardiac output and peripheral resistance. As the disease progresses and renal function deteriorates, both cardiac output and peripheral vascular resistance increase, the latter disproportionately.[10,11] Volume dependency is easily observed in patients with severe proteinuria and glomerulonephritis. Patients with predominantly interstitial disorders, such as tubulointerstitial nephritis and medullary cystic disease, do not retain salt and water. They do not develop hypertension until late in the course of their disease when they may retain salt and water.

Rationale for Therapy

Many hypertensive patients with renal insufficiency are not treated because of reluctance to lower perfusion to already compromised kidneys. The old adage that blood pressure should not be lowered if the blood urea nitrogen is higher than 40 mg./dl. was disproved by Moyer et. al., who demonstrated that renal function stabilized when this was done.[13,14] While aggressive therapy of hypertension in patients with abnormal renal function may result in temporary decline of renal function, most will show stabilization or improvement in renal function with continued treatment.[15-24] In some patients, uremia does occur during therapy, and dialysis may be required. Even then, however, return of renal function is occasionally seen.[25] Preliminary data from diabetic patients with significant nephropathy and severe hypertension suggest that the predicted decline in glomerular filtration rate from the 17th to the 20th year of insulin therapy can be retarded by strict control of hypertension.[26] These studies suggest that the vascular necrosis, myointimal cell proliferation, and necrotizing arteriolitis of malignant accelerated hypertension are potentially reversible if aggressive therapy is instituted.[27] Long-term follow-up of patients with milder renal abnormalities have shown elimination of proteinuria and improvement in renal function with effective blood pressure control.[24,28,29]

TABLE I. CLINICAL USE OF ANTIHYPERTENSIVE DRUGS IN PATIENTS WITH RENAL INSUFFICIENCY

1)	Diuretics Ethacrynic acid, furosemide, metolazone
2)	Sympatholytics Clonidine, methyldopa, prazosin, beta blocking agents
3)	Vasodilators Hydralazine, minoxidil
4)	Angiotensin blocking agents Captopril

EVALUATION OF THE PATIENT

In addition to the complete evaluation that should be performed for any hypertensive patient, two major areas are important for therapy and outcome. The first is thorough evaluation of the patient's fluid status by history and physical examination. A careful assessment of renal function, including a creatinine clearance, is also needed to evaluate the choice of therapy and its effects. For example, when excessive fluid retention and severe renal dysfunction are present, dialysis may be the only therapy available.

THERAPEUTIC GUIDELINES

The basic aim is to reduce the elevated blood pressure to normal in lying and standing positions using a regimen that provides the patient with minimum side effects. Most hypertension associated with renal disease is volume dependent. The first thrust of treatment should be to diminish volume excess through the use of dietary sodium restriction, diuretic therapy, or both. Other medication is then added as required (Table I).

DIETARY SODIUM RESTRICTION

Salt restriction is a mainstay of therapy for patients with benign essential hypertension who have normal renal function. Patients with hypertension and renal disease likewise can benefit from it because they often are prone to salt and water retention. Most patients with renal insufficiency (other than proved salt wasters) can maintain renal perfusion on a modestly sodium restricted diet if their kidneys are given time to adapt to their new environment.[30-36] Severe acute salt restriction, however,

TABLE II. DIURETICS AND RENAL DISEASE

Serum creatinine less than 2.5 mg./dl. or creatinine clearance more than 30 cc./min.
Thiazides
Metolazone (Diulo, Zaroxolyn)
Furosemide (Lasix)
Ethacrynic acid (Edecrin)
Acetazolamide (Diamox)
Sprionolactone (Aldactone)
Triamterene (Dyrenium)
Serum creatinine greater than 2.5 mg./dl. or creatinine clearance less than 30 cc./min.
Metolazone (Diulo, Zaroxolyn)
Furosemide (Lasix)
Ethacrynic acid (Edecrin)

should be avoided in these patients unless they have significantly expanded fluid volumes or have the nephrotic syndrome because it may cause decreased plasma volume, dehydration, and subsequent deterioration of renal function that may become irreversible.[30-34]

DIURETIC AGENTS

If modest dietary sodium restriction alone is ineffective in controlling the blood pressure, diuretics are indicated. The thiazide diuretics may not cause a natriuresis in patients with serum creatinines above 2.5 to 3 mg./dl. More potent diuretics, such as furosemide, ethacrynic acid, and metolazone, still retain some effect if given in sufficient quantity.[37-40] Doses of these diuretics required to achieve natriuresis usually are proportional to the degree of renal insufficiency but they may be higher than those customarily used, e.g., furosemide, up to 800 mg./daily. If the hypertension is accompanied by severe edema, combinations of a loop diuretic and metolazone may be necessary.[41] Potassium sparing diuretic agents, such as spironolactone, triamterene, or amiloride, are contraindicated in the presence of azotemia because of the danger of hyperkalemia and metabolic acidosis. If circulatory volume depletion is carried to the point of orthostatic pressure changes or renal function deterioration without satisfactory blood pressure control, additional medication is required (Table II).

SYMPATHOLYTIC AGENTS

The next group of drugs that we customarily use in the treatment of

TABLE III. GUIDELINES IN THE MANAGEMENT OF PATIENTS WITH HYPERTENSION AND RENAL DISEASE

1)	Note clinical fluid status (weight)
2)	Restrict dietary sodium intake slowly
3)	Begin diuretic according to renal function and fluid retention
4)	Increase diuretic until: a) Blood pressure is controlled, or b) Mild orthostatic change achieved, or c) Renal function decreases significantly
5)	If blood pressure is not controlled, begin additional antihypertensive drugs
6)	Recheck renal function frequently

hypertension is also effective in patients with renal disease. It includes methyldopa, clonidine, and all the beta-blocking drugs. While there have been some reports that these drugs experimentally cause some decrease in renal blood flow, experience has shown that this has not been a clinical problem. Customary doses should be used without exceeding the usual maximal doses, even in advanced renal insufficiency. The end point of therapy is the control of blood pressure.

OTHER AGENTS

If dietary sodium alterations, diuretics, and sympatholitic agents are ineffective, then other drugs should be added to control the blood pressure, such as hydralazine, minoxidil, and prazosin.[42-47] Hydralazine and minoxidil are vasodilators that do not adversely affect renal function, although minoxidil may cause such a marked increase in salt and water retention that an increase in diuretic doses may be required.[46-47] Prazosin is an alpha-adrenergic antagonist which is also effective without diminishing renal function.

Ganglionic blocking agents such as guanethidine should not be used in patients with renal insufficiency because their action depends upon decreasing venous return to the heart, causing diminished cardiac output with a consequent decrease in renal plasma flow and glomerular filtration rate.

Angiotensin converting enzyme inhibitors, such as captopril, may prove valuable, especially in those patients with renin dependent hypertension and renal disease. If used, the dose should be lowered because of the prolonged half-life. Because these agents have just become available, long term studies in patients have not yet been performed. Caution should, therefore, be exercised in their use.

SUMMARY

Hypertension frequently accompanies renal disease, whether or not impaired renal function is present. This hypertension is most often volume dependent because of salt and water retention. After an initial assessment of volume status and renal function, modest dietary sodium restriction and diuretics are useful first steps in treatment. If blood pressure control is not satisfactory, other antihypertensive agents should be utilized (Table III) in a stepwise fashion. Renal function should be reassessed frequently as the blood pressure is being normalized.

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